Quality Assurance Oversight Plan

Quality Assurance Group Mission

To provide exceptional quality assurance and quality improvement (QA/QI) services to Principal Investigators that are also acting as the Sponsor (i.e., Sponsor-Investigator[1]) for drug and device clinical trials at the University of Utah and, upon request, any clinical research study across the University.

Quality Assurance Group (CRSO QA) Vision

2021- 2024

1. Required monitoring service for all University of Utah Sponsor-Investigators (SI) holding an Investigational New Drug (IND) Application or Investigational Device Exemption (IDE) with the U.S. Food & Drug Administration (FDA), per *Table 1. Sponsor-Investigator Monitoring Frequencies*
2. Mandatory FDA audit preparation and guidance for research teams
    a. Required on-site assistance with FDA investigator inspections
3. Optional non-FDA audit preparation and guidance for research teams
4. University networking and collaboration: conduct an annual review of at least 1 study from each school/college
5. Develop QA/QI tracking and metrics systems

2025-2027

1. Monitoring service for national and industry trials conducted at the University of Utah
2. Provide QA/QI services to University of Utah network studies that have external participating sites
3. Expand QA/QI services to all studies conducted at the University of Utah

2028

1. National leader in academic clinical trials QA/QI structure, with publications and regular presentations at national and international meetings

[1] See *21 CFR 312.3*: "*Sponsor-Investigator* means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor."

University of Utah Sponsor-Investigator studies with an IND/IDE

1. To protect the University of Utah and its Sponsor-Investigators: all investigators who hold an IND/IDE will be **required** to utilize the CRSO monitoring services, as described below in item 2. Exemptions to this requirement are possible under the following conditions:
    i) Studies monitored by the Huntsman Cancer Institute's (HCI) Research Compliance Office
    ii) Additional exemptions may be possible on a per trial basis upon review of the trial's monitoring plan by the CRSO QA Team
2. The CRSO QA group will conduct required monitoring of all University of Utah Sponsor-Investigator studies with an IND/IDE at the following timepoints:
    i) Following first participant enrollment
    ii) Routine monitoring, as determined by *Table 1. Sponsor-Investigator Monitoring Frequencies*
3. Reviews may involve one or more of the items listed below in *Table 2*
4. Reviews may be conducted on-site, remotely through a secure web-platform, or a combination of both. The review method will be determined with the study team prior to review.
    a. Reviews may include study-team completion of a self-assessment, as needed to expedite audit preparation, identify at-risk studies for full monitoring, support risk-based monitoring by the CRSO, and/or to educate and develop self-compliance within study teams.
5. The following list specifies how the CRSO QA services will be implemented and utilized:
    i) The Clinical and Translational Science Institute (CTSI) REDCap Intake form needs to be completed before CRSO QA services can begin. The form can be accessed directly here, or by clicking on the "Request Services (PROTRACKS)" in the top banner of the CRSO webpage.
        a. If you have already completed the REDCap Intake form, please send an email to crsoqa@hsc.utah.edu for assistance in requesting monitoring support.
        b. If you have not already completed the REDCap Intake form and you send an email to crsoqa@hsc.utah.edu, you will be instructed to compete the Intake form to begin the process.
    ii) Prior to submitting an IRB new study application for a University IND/IDE Sponsor-Investigator trial, the Principal Investigator (PI) may utilize the CRSO QA for additional services listed below in *Table 3. CRSO QA Additional Services*, such as protocol development assistance, protocol risk assessment, and monitoring plan development assistance.
    iii) The IRB-approval letter will inform PIs and study teams that the CRSO QA group will monitor the study following first enrollment. It is the responsibility of the Sponsor-Investigator to notify the CRSO QA group (crsoqa@hsc.utah.edu) upon

enrolling the first study participant. The CRSO QA group will also generate first enrollment reports through OnCore for applicable studies to ensure first-participant monitoring occurs.

iv) After the first-enrollment review is completed, an ongoing required monitoring schedule will be established, in accordance with *Table 1* (below).

v) For IND/IDE Sponsor-Investigator trials already IRB-approved and active, the CRSO QA will contact the trial PI to initiate the group's monitoring services.

6. The baseline scope and frequency of the monitoring services listed above for an individual trial will be determined with a CRSO QA trial risk assessment prior to initial review.
    i. The trial risk factors used to determine baseline monitoring scope and frequency may include, and are not limited to: the phase of the trial, trial complexity, enrollment goals, multi-site trial, and/or investigator and trial team experience.
7. The monitoring scope and frequency is dynamic throughout the life of the trial. The frequency and/or scope may increase or decrease throughout the trial based on performance and needs of the investigative team (see *Table 1*, below).
8. The Sponsor-Investigator will be given a monitoring summary report and letter at the conclusion of each visit. The documents will outline any significant findings or concerns, potential plans for remediation, if necessary, and the timeline for the next expected monitor review.
9. The Associate Dean for Clinical Research, medical director of the CRSO, or senior leadership of the CTSI may mandate and initiate site monitoring of any research at their discretion.

All University of Utah Investigators and Study Teams

1. The CRSO QA team provides several services to **all** University of Utah Principal Investigators (PI) and study team, detailed below:
    i. In the event of becoming aware of an upcoming FDA Audit, the PI and study team are **required** to notify the CRSO QA Team immediately by telephone or email notification (801-646-5925; crsoqa@hsc.utah.edu). Email notification should be copied to the Associate Dean for Clinical Research (mike.dean@hsc.utah.edu). The CRSO QA team will provide mandatory support in preparation for the audit as well as support during the audit.
    ii. PI's and study teams that are being audited by a non-FDA entity (e.g., IRB, sponsor) have the **option** of requesting support and/or guidance from the CRSO QA team in preparation for the audit. Support can be requested through completion of the REDCAP Intake form (see item #2, below).
    iii. A PI or study team may identify specific study aspects effecting quality and/or compliance that they would like assistance resolving. Topics include deviation reporting, Corrective and Preventative Action Plan (CAPA) creation and resolution, source data review, Case Report Form (CRF) management, training, and other

activities (see *Table 3*, below). These services can be requested through the REDCAP intake form (see item #2, below).

2. Reviews may be conducted on-site, remotely through a secure web-platform, or a combination of both. The review method will be determined with the study team prior to review.
    i. Reviews may include study-team completion of a self-assessment, as needed to expedite audit preparation, identify at-risk studies for full monitoring, support risk-based monitoring by the CRSO, and to educate and develop self-compliance within study teams.
3. Please remember that the Clinical and Translational Science Institute (CTSI) REDCap Intake form needs to be completed before CRSO QA services can begin. The form can be accessed directly here, or by clicking on the "Request Services (PROTRACKS)" in the top banner of the CRSO webpage.
    i. If you have already completed the REDCap Intake form, please send an email to crsoqa@hsc.utah.edu for assistance in requesting monitoring support.
    ii. If you have not already completed the REDCap Intake form and you send an email to crsoqa@hsc.utah.edu, you will be instructed to compete the Intake form to begin the process.
4. Regardless of sponsorship type or the timeline established in the CRSO QA Vision, the Associate Dean for Clinical Research, medical director of the CRSO, or senior leadership of the CTSI may mandate and initiate site monitoring of any research at their discretion.

Table 1- Monitoring Frequencies[1]				
Study Type	Internal Risk Category	Default Monitoring Frequency	Reduced[2] Monitoring Frequency	Increased[2] Monitoring Frequency
Sponsor-Investigator, therapeutic	High	• *First participant*: as determined by a review of the protocol SOE[3] and monitoring plan • *Standard Routine*: all new and active participants at 6-month intervals	*Reduced Routine*: all new and active participants annually	*Increased Routine*: all new and active participants at 3-month intervals
Sponsor-Investigator, interventional but non-therapeutic	Moderate	• *First participant*: as determined by a review of the protocol SOE[3] and monitoring plan • *Standard Routine*: all new and active participants annually	*Reduced Routine*: all new and active participants annually	*Increased Routine*: all new and active participants at 6-month intervals
Sponsor-Investigator, non-interventional	Low	• *First participant*: as determined by a review of the protocol SOE[3] and monitoring plan • *Standard Routine*: new participants as needed if any of the first four "other factors" below[4] are met	N/A	*Increased Routine*: all new and active participants on treatment annually
National or Industry, therapeutic[5]	High	• *First participant*: as determined by a review of the protocol SOE[3] and monitoring plan • *Standard Routine*: new participants as needed if any of the first four "other factors" below[4] are met	N/A	N/A
National or Industry, interventional but non-therapeutic[5]	Moderate	• *First participant*: as determined by a review of the protocol SOE[3] and monitoring plan • *Standard Routine*: new participants as needed if any of the first four "other factors" below[4] are met	N/A	N/A
National or Industry, non-interventional[5]	Low	Not internally monitored	N/A	N/A

1. The following are not monitored by CRSO QA: informed-consent exempt, and studies that are monitored by the Huntsman Cancer Institute's (HCI) Research Compliance Office
2. Monitoring frequencies are evaluated at the conclusion of each monitoring review and are based on performance and needs of the investigative team
3. SOE = Schedule of Events
4. Other factors:
    a. Pending Sponsor or Regulatory agency audit
    b. Trial closure by Sponsor
    c. Critical data or process deviations
    d. Departmental/divisional requests

e. Junior trial personnel staff
f. Change in safety profile
g. Issues noted by DSMB/Data Management Committee
h. PI change
i. Unresolved issues following internal monitoring visit(s)
j. Increase in number of monitoring action items

5. Per the CRSO QA Oversight Plan, National and industry studies will be monitored starting in 2025

Table 2 – What may be reviewed during a monitoring visit?
• Consents and consenting process
• PI Oversight of study conduct
• Eligibility criteria
• Subject source documents, including the medical record
• Investigational Product (IP) accountability
• Primary endpoint and critical data source review and verification
• Safety and deviation assessment and reporting
• Regulatory Essential Documents
• Suspected unexpected serious adverse reactions (SUSARs)
• Other items as needed depending on the complexity of the trial

Table 2. Scope of the CRSO QA monitoring services, which may be reviewed at each monitoring visit.

Table 3 – CRSO QA Additional Services (as Requested and Approved)
• Protocol review, input, and edits
• Protocol risk assessment
• Protocol monitoring plan review, input, and edits
• Ongoing coordinator Q&A
• Case Report Forms review, input, edits
• Deviation reporting consultation and assistance
• Deviation root cause analysis and CAPA consultation and assistance
• Source data review and verification (EDC review and verification)
• Training regarding any of the topics listed in Table 1 and 2, and others, as determined.

Table 3: Additional services provided by the University of Utah CRSO QA Group on a case-by-case basis.

CRSO QA Monitoring- What to Expect

Pre-Visit

1. The CRSO team will work with study staff to schedule dates for the monitoring visit.
2. Once dates have been mutually agreed upon, the CRSO team will send a confirmation letter to the PI and study staff with the monitoring visit dates and which binders/charts will be reviewed.
3. If the visit is conducted on-site, we will need a room large enough for the required number of monitors which will be confirmed in the confirmation letter, enough desk space to lay out multiple binders/charts, and internet/Wi-Fi access.
4. If the visit is conducted remotely, we will need access to all locations (for example, Ubox folders) where documents are stored.
5. If the visit is conducted or supplemented by Self-Assessment, the CRSO QA team will invite the responsible investigator and study team to complete a Self-Assessment through the IRB-portion of the Electronic Research Integrity & Compliance Administration system (ERICA).

Pre-Visit Preparation Tips

1. Participant and Regulatory documents should be maintained in a review-ready state at all times.
2. The CRSO QA reviews participant and Regulatory charts/binders for completeness and compliance; the CRSO QA monitors do not perform EDC data verification.
3. Ensure the charts/binders are well organized: file loose pages; repair torn hole punches; separate into multiple binders rather than over-stuffing; maintain a consistent filing system within the same study.
4. Use tabs to separate visits/cycles, logs, consents, etc. and label tabs clearly (use Sponsor-provided tabs, if applicable).
5. Ensure documents needing PI signatures are signed and dated.
6. Ensure documents contain clear attribution: if more than one person is filling out a document/form, ensure each attribution is noted, initialed, and dated.
7. Ensure all external monitoring reports/letters are filed in the Regulatory binders.
8. If applicable, a Self-Assessment Checklist will be completed within ERICA by the study team. The responsible investigator will submit the Self-Assessment Checklist for review by the CRSO QA.

Visit

1. All findings/queries will be documented in a query report.
2. When all binders/charts have been reviewed, the CRSO monitor(s) will schedule a meeting with applicable study staff, managers, and possibly the PI.
3. The CRSO QA team will make recommendations for resolving findings/queries, and may follow-up on significant findings, as needed. However, responsibility for final resolution rests with the PI and study staff.
4. If applicable, CRSO QA will review the completed Self-Assessment within ERICA.

Post-Visit

1. The CRSO QA team will determine the frequency of ongoing, routine monitoring visits (as described in *Table 1*) based on visit findings.
2. The CRSO QA team will draft a summary letter indicating the dates of the monitoring visit, participant numbers, documents reviewed, and planned frequency for future reviews.
3. The CRSO QA team will send the summary letter and query report to the PI and study staff.
4. The PI and study team should review findings and implement appropriate resolutions as needed.